## REMARKS / ARGUMENTS

Claims 1, 3, and 4 are pending in the instant application. Claims 1 and 4 are amended in the instant correspondence. Applicants, in order to further business interests and without acquiescing to any argument presented by the Examiner while expressly reserving the right to prosecute same (or similar) claim in subsequently filed applications, have cancelled pending claim 3 without prejudice.

Claims 1, 3, and 4 were rejected in the final office action mailed on June 17, 2003. The Examiner made the following rejections:

(1) The Examiner objects to the figure legend of selected drawings.

(2) Claims 1, 3, and 4 were rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. patent 4,762,779 to Snitman in view of U.S. patent 6,255,476 to Vinayak *et al.*

The Applicants believe the present amendments, and the following remarks, traverse the Examiner's rejection of the pending claims. These remarks are presented in the same order as they appear above.

**(1) Applicants' Figures Do Not Illustrate The Prior Art**

Once again, the Examiner maintains that Figures 1A, 1B, 2A and 2B should be labeled, in the figure legend, as prior art. The Examiner alleges the Applicants have admitted, in the specification of the application as filed, these figures describe that which is already known in the art. The Applicants have made no such admission and, moreover, the chemistries presented in these figures are clearly not contemplated by the prior art.

The Examiner alleges that Figures 1A and 1B illustrate the "prior art" based on the following excerpt from the specification,

> "[c]urrently available technologies for the attachment of 5' end labels to synthetic oligonucleotides rely on two general approaches. The most popular approach requires of the production of phosphoramidite derivatives of the desired label and subsequent coupling to a support-bound protected oligonucleotide *via* standard oligonucleotide synthesis techniques. This process is exemplified in Figures 1A and 1B, which shows the synthesis of a tetramethylrhodamine (TMR) labeled oligonucleotide."[1]

While Figures 1A and 1B may exemplify an overall synthetic approach familiar to one of skill in the art, the *Applicants have not admitted the specific chemistries, projected in these figures, are described in the prior art.* Indeed, in subsequent sections of the specification, the Applicants recite (with specificity) aspects of these chemistries which are completely distinct from the prior art. For example, the Applicants teach that (as shown in Figure 1A):

> "[f]ollowing the activation of the carboxyl functional group, the *tetramethylrhodamine is reacted with a bifunctional linker arm, in this case N-methylaminoethanol.* Such a linker arm serves several functions. It provides needed distance between the label and the oligonucleotide, a functional group, in this case an amine; appropriate for reaction with the tetramethylrhodamine and a functional group, in this case a hydroxyl, which will ultimately allow for the coupling to the 5' hydroxyl of a support-bound protected oligonucleotide."[2] (emphasis added)

That is to say, in Figure 1A a methyl group is added to an omega amino phosphoramadite to yield a complexed TMR capable of fluorescing. If a TMR was incorporated with an omega amino phosphoramadite lacking this methyl group, the resulting complex would then further react to form a derivative that does not fluoresce. In this respect, the compositions and chemistries shown in Figures 1A are distinct from protocols described in the prior art.[3]

Furthermore, as noted by Applicants in their office action response dated March 31, 2003, the chemistries applied to the Tetramethyl Rhodamine (TMR) (used in the reactions recited in Figures 1A and 1B) are distinct from labeling traditional labeling approaches as they avoid unstable acid labile intermediates inherent with "standard" labeling techniques described in the prior art.

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[1] Page 11, ll. 9-14 of the application filed on June 28, 2001.

[2] Id. at page 11, ll. 15-24.

[3] Including, but not limited to, the labeling protocols presented in U.S. patent 4,762,779 to Snitman (a reference cited by the Examiner in support of the pending rejection under 35 U.S.C. §103).

With respect to Figures 2A and 2B, the excerpt from the specification quoted by the Examiner is *an affirmation* that the synthetic schemes projected in these figures are *different* from the prior art. The Applicants state,

> "[a] two-step variation of this approach is used only in cases where the corresponding phosphoramidite is not available. This approach is exemplified in Figures 2A and 2B, which illustrate the approach using TMR as the labeling compound."[4]

Specifically, this variation is in reference to the synthetic schemes presented in Figures 1A and 1B. Given the Applicants have demonstrated that chemistries recited in Figures 1A and 1B are not described by the prior art then, by definition, "variations" on these same chemistries may not be properly categorized as prior art. Moreover, as previously noted by Applicants in their office action response dated March 31, 2003, the reaction schemes presented in Figures 2A and 2B project two distinct coupling processes not described by the prior art.

In sum, *Applicants have not admitted* the chemistries presented in Figures 1A, 1B, 2A and 2B are equivalent to any protocol described in the prior art. Applicants have documented how the chemistries in these figures are divergent from protocols known in the art the time the instant application was filed. Applicants also note the Examiner, in the office action mailed June 17, 2003, again fails to provide any *specific examples* which illustrate how the chemistries, presented in the figures in question, are identical to anything in the prior art. Since the Applicants have made no admissions (regarding the parity of the chemistries projected in these figures and the prior art) and the Examiner provides no evidence (beyond the improperly constructed excerpts from the specification discussed above); the Applicants decline to label any of the pending figures as "prior art" and respectfully request the Examiner withdraw his objections [raised under MPEP §608.02(g)] to these figures.

**(2) The Claims Are Not Obvious Under 35 U.S.C. § 103(a)**

In their correspondence mailed March 31, 2003 the Applicants provided a detailed analysis as to how the Examiner failed to make a *prima facie* case of obviousness with regard to U.S. patent 4,762,779 to Snitman in view of U.S. patent 6,255,476 to Vinayak *et al.* Specifically, the Applicants documented how: i) the Examiner failed to provide any evidence

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[4] Page 12, ll. 3-14 of the application filed on June 28, 2001.

which would motivate the combination (of the cited references) to teach the claimed invention which describes, in part, the use of bifunctional linker arms and *in situ activated labels* in methods which produce a labeled support-bound protected oligonucleotide.

In response the Examiner states that, "[in] this case, the motivation to combine the reference is based the knowledge [sic.] gained from the combined teaching of Snitman and Vinayak *et al.*"[5] Upon close inspection, however, the knowledge which *allegedly motivates the combination* of these references is the Examiner's own conclusion which are annotated with non-dispositive excerpts from the cited art.

For example, the Examiner states that,

> "Snitman *et al.* teach a phosphoramidite linker with the formula [ ], which only differs from the claimed linker for having a methyl moiety on the phosphate oxygen instead of the cyanoethyl moiety. Vinayak *et al.* also teach a phosphoramidite linker (col. 11, structure 8 when R is cyanoethyl) with very similar structure to the claimed linker (especially the first one) except it has only one methoxy moiety."[6]

As a threshold objection, Applicants note that the pending claims are directed to methods of labeling oligonucleotides and not compositions of matter. That is to say the Examiner's "obviousness" analysis is confined to alleged similarities, between the cited art and the invention as claimed, of a *single reagent*[7] and not the method (as claimed) of labeling oligonucleotides of which this reagent is a component.

With regard to the claimed methods of the present invention, the Examiner once again presents bald conclusions in place of reasoned motivation, as demanded by the Federal Circuit, to combine the cited art. Specifically, the Examiner states that,

> "[b]ased on the reaction chemistry disclosed in the references, it would have been obvious to one of ordinary skill in the art that variation such as one methoxy group instead of two, or having methyl instead of cyanoethyl at that position does not affect the ability for the linker's function as long as it can undergo beta-elimination. . .[t]herefore, the claimed invention is *prima facie* obvious to one of ordinary skill in the art at the time the invention was made."

In this respect the Examiner appears to suggest that, with the aid of hindsight, the art appears combinable or modifiable in a manner that will yield the claimed invention. The Examiner is

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[5] Office action mailed June 17, 2003, page 4.

[6] *Id.*

[7] e.g. the phosphoramidite linker.

reminded, however, that *the art must still suggest* the desirability of the modification. See, *In re Gordon,* 733 F.2d 900, 902, 221 USPQ 1125, 1127 (Fed. Cir. 1984). The references cited by the Examiner make no such suggestion. That is to say, the prior art provides no motivation to combine the references to teach the claimed invention which describes, in part, the use of: i) the claimed bifunctional linker arms, ii) the specifically claimed *in situ* unactivated labels[8] (which is subsequently reacted to create an *in situ* activated label) in a method which produces a labeled support-bound protected oligonucleotide.

Instead of pointing to a specific teaching in the cited art (or any other piece of accepted evidence) regarding the claimed labeling methods, the Examiner substitutes an "obvious to try" standard in support of the pending rejection under 35 U.S.C. § 103(a). However, in moving from the prior art to the claimed invention, the Examiner is not free predicate a determination of obviousness on what the skilled person might try or find obvious to try. See, for example, *In re Geiger*, 2 USPQ 2d 1276, 1278 (Fed. Cir. 1987). With regard to the invention as claimed in the instant application, the Examiner fails to show how the alleged parity of one reagent (*i.e.* the phophoramidite linker) renders obvious the *methods* as claimed. Therefore, because the cited references (even if improperly combined) fail to disclose *all* the limitations of independent claims, a *prima facie* case of obviousness has not been made. Applicants respectfully request, therefore, the pending rejections under 35 U.S.C. § 103(a) be withdrawn.

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[8] Without acquiescing to any argument presented by the Examiner, and in order to further their business interest without prejudice to prosecuting the claims as originally filed (or claims similar thereto) Applicants have amended pending independent claims 1 and 4 to recite, in part, an *in situ* unactivated labels selected from compounds presented in Tables 1-3 in the application as filed (see, pp. 16-18). In addition Applicants have amended the claim element "bifunctional linker arm" such that it now recites, "a bifunctional linker comprising a hydrocarbon, a protected secondary amine, and a hydroxyl group." Support for this amendment is provided by the chemical structures of the "Linkers" provided in Table 2 (on page 16 of the application as filed) and on page 2, ll. 12 - 15 of the application as filed.

## CONCLUSION

Applicants submit the arguments set forth above traverse the Examiner's rejections and, therefore, request that these rejections be withdrawn for the reasons set forth above. Should the Examiner believe a telephone interview would aid in the prosecution of this application, Applicants encourage the Examiner to call the undersigned collect at 617.984.0616.

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Thomas W. Brown
Registration No. 50,002

MEDLEN & CARROLL, LLP
101 Howard Street, Suite 350
San Francisco, California 94105
617.984.0616